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An extracellular matrix graft (Oasis® wound matrix) for treating full-thickness pressure ulcers: A randomized clinical trial

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ABSTRACT

Aim: The purpose of the study was to evaluate clinical safety and effectiveness of Oasis® Wound Matrix as a treatment for full-thickness pressure ulcers and compare it to Standard Care.

Methods: A total of 130 adults with Stage III or Stage IV pressure ulcers were randomly assigned, received either multiple topical treatments of SIS plus standard care (n = 67), or standard care alone (n = 63), and were subsequently evaluated. Ulcer size was determined at enrollment and weekly throughout treatment. Healing was assessed at each visit for a period of up to 12 weeks, with incidence of complete healing and 90% reduction in ulcer area being the primary outcome measures.

Results: The proportion of complete healing in the SIS group was 40% as compared to 29% in the standard of care group (p = 0.111); the percentage of patients having a 90% reduction in ulcer surface area was 55% in the SIS group versus 38% in the standard of care group (p = 0.037).

Conclusions: The results of this study suggest that within the setting of a comprehensive wound care program, weekly treatment of chronic pressure ulcers with SIS wound matrix increases the incidence of 90% reduction in wound size versus standard of care alone.

1. Introduction

Pressure ulcers are a prevalent clinical problem in the elderly and spinal-cord injured populations, annually afflicting approximately 2–3 million people in hospitals and nursing homes [1–4]. Historically, pressure ulcers have been referred to as pressure sores, bedsores and decubitus ulcers. In 2016, the National Pressure Ulcer Advisory Panel [5] changed the term "*pressure ulcer*" to "*pressure injury*" to describe pressure injuries to both intact and ulcerated skin. However, in 2017, in a regulatory ruling by the Center for Medicare and Medicaid Services (CMS) in the United States, definitions were further clarified. Open wounds caused by pressure are defined as "ulcers" and wounds with intact skin are defined as "injuries" [6]. This paper will utilize the term "pressure ulcer" as currently defined by the CMS.

Pressure ulcers can develop in any setting where an individual remains in one position (such as prone or sitting) for a prolonged amount of time [7]. Patients who develop pressure ulcers suffer pain and discomfort, have longer hospitalization and rehabilitation times, and often require prolonged, ongoing ulcer care outside the hospital and in long-term care facilities [8]. This prolonged ulcer care also extends into the Home Health Care and Outpatient Wound Clinic settings. Resulting costs to the healthcare system have been estimated at over $9.1 billion annually, much of which is borne by publicly-subsidized programs [3,8,9].

The standard, non-surgical treatment for a clean, full-thickness pressure ulcer is wound cleansing followed by the placement of a topical dressing to provide for a moist wound healing environment; pressure redistribution; elimination of drainage; and supportive care [2]. In these wounds, six-month healing rates of only 40–45% for Stage III ulcers and 31–34% for Stage IV ulcers have been reported [10,11]. Finding affordable, alternative treatment options that are more effective than currently available therapies would therefore have benefits in terms of reduced treatment costs and reduced patient morbidity.

Significant advances have been made in the development of alternative therapies for the treatment of pressure ulcers of various etiologies. One such advancement, the use of the extracellular matrix derived from natural animal tissue to promote granulation and epithelization, has shown efficacy versus standard of care in the treatment of venous wounds [12,13] and diabetic ulcers [14]. This product, a biomaterial derived from the pig small intestine submucosa (SIS, OASIS® Wound

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Matrix, Cook Biotech Incorporated, West Lafayette, IN), has been extensively evaluated in pre-clinical models and in clinical use since its unique properties were first reported in 1989 [15]. SIS is a thin, translucent layer of the intestine, is approximately 0.10–0.15 mm thick and consists primarily of a collagen-based extracellular matrix (ECM). However, unlike other purified collagen wound care products, other components of the ECM, such as glycosaminoglycans (i.e., hyaluronic acid), proteoglycans, fibronectin, and other matrix-associated factors, including basic fibroblast growth factor and transforming growth factor-beta are retained in bioactive forms [16–19].

In this study, the efficacy of the SIS wound matrix in promoting wound closure was evaluated in patients with Stage III and Stage IV full-thickness pressure ulcers. The hypothesis was that treatment of full-thickness pressure ulcers with the SIS wound matrix in addition to standard care would lead to a greater proportion of healed ulcers (90% and 100% closed) at 12 weeks versus standard of care alone. We present a randomized human clinical trial to assess the effectiveness of the SIS wound matrix in the treatment of these debilitating wounds.

2. Methods

2.1. Test material

The SIS Wound Matrix is a naturally-occurring extracellular matrix derived from the submucosal layers of the porcine small intestine. It is processed into an acellular template into which the patient's cells can grow, and is comprised of collagen and other extracellular matrix factors, including glycosaminoglycans (i.e., hyaluronic acid), proteoglycans, fibronectin, and growth factors, such as basic fibroblast growth factor and transforming growth factor-beta [16–19]. The SIS wound matrix undergoes rigorous controlled processes to remove contaminants, provide sterility, and ensure that any possible transmissible viruses are inactivated [20].

2.2. Study design

This randomized, open-label, controlled clinical trial conducted at 12 institutions across the United States enrolled 130 patients. Patients over 18 years old were randomly assigned to one of two treatment arms. Treatment arm one consisted of the control standard-of-care treatment, including dressing changes, wound cleansing, wound debridement as needed and wound coverage with isotonic gel and semi-occlusive absorbent film dressings. Treatment arm two consisted of the application of SIS wound matrix in addition to the control standard-of-care treatment. All patients in each group were on appropriate pressure redistribution support surfaces; either a dynamic or static air mattress overlay or full dynamic air mattress. Patients were followed weekly for up to 12 weeks or until complete healing occurred. A six-month follow-up visit was also requested.

2.3. Study population

This trial was conducted in the United States in full accordance with the international standards of Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. The study protocol and informed consent statements were reviewed and approved by either an independent institutional review board (IRB) or each study location's governing IRB. Prospective patients who presented with a Stage III or Stage IV pressure ulcer [2], as diagnosed by clinical presentation, and who signed the informed consent form, were considered for inclusion if they were on a pressure-reducing support device and met the additional criteria presented in Table 1.

Patients were excluded from the trial for any of the following: wounds with heavy or high volume exudate; eschar; significant arterial disease (ankle-brachial index (ABI) less than 0.60); any known medical condition known to impair wound healing (including, but not limited to: malnutrition (Albumin < 2.5 mg/dL), cellulitis, osteomyelitis, necrotic or avascular ulcer beds, uncontrolled diabetes ($HgbA_{1c}$ > 12%), or sickle cell disease); taking concomitant medication known to impair wound healing (corticosteroids > 10 mg daily, immune suppressives); a history of radiation therapy to the wound site, allergy to porcine products; clinical signs of infection at the target ulcer; undergoing hemodialysis; or having religious or cultural objections to the use of porcine products.

Table 1
Summary of patient inclusion criteria.

Variable	Criteria
Patient Age	≥18 years
Ulcer Size	1–64 cm^2
Ulcer Depth	≤1.5 cm
Undermining/tunneling	≤1.5 cm
Wound Bed Characteristics	Viable wound bed with at least 80% granulation tissue

2.4. Randomization

Eligible patients were assigned to a treatment group using a centralized computer system that randomly assigned patients to one of the two treatment arms. The system was designed to assign patients from each study site to balanced arms using a block randomization scheme with a block size equal to 4. Investigators were blinded to this randomization scheme to eliminate bias and, upon contacting the computer system, received an automatic faxed confirmation that indicated the patient's assigned group and unique enrollment number.

2.5. Protocol and evaluations

Following treatment initiation, patients were evaluated weekly for up to 12 weeks. At baseline and each follow-up visit, ulcer healing was evaluated and recorded by photographs and wound measurements. Ulcer length was defined as the longest edge-to-edge measurement of the ulcer, width was measured at the widest point perpendicular to the length, and depth was the deepest vertical measurement using a cotton tip swab.

Patients in both groups received weekly standard of care treatments which included wound cleansing, debridement as clinically indicated, and dressing changes. During each dressing change, wounds were cleansed with normal saline solution and covered with isotonic saline gel [Normlgel®, Molnlycke Health Care] followed by a semi-occlusive absorbent film dressing [Alldress®, Molnlycke]. SIS was applied directly to the wound bed only in the SIS wound matrix treatment group followed by standard of care treatment and was reapplied at weekly intervals. Before applying the SIS wound matrix, the pressure ulcer was routinely cleansed with normal saline solution, the SIS was cut to size slightly larger than the ulcer and placed upon the wound bed. The SIS was covered with isotonic saline gel to maintain a moist healing environment and then secured using a semi-occlusive absorbent film dressing. The patients remained on the pressure redistribution support surface that they were on at initial study visit.

Demographic and baseline data collected included patient gender, race, age, weight, height, baseline glycosylated hemoglobin ($HgbA_{1c}$), baseline albumin, and patient location (long-term care, outpatient, or home care). Baseline ulcer information included ulcer location, duration, status (new or recurrent), stage and surface area. Baseline medical history information included patient status on each of the following: Type I diabetes, Type II diabetes, connective tissue disease, immunosuppression, peripheral vascular disease and dementia. In addition, baseline levels of granulation tissue and avascular tissue along with the baseline debridement status and the amount of drainage were recorded. Baseline characteristics were used as covariates in the final

statistical analysis to judge their influence on treatment success.

Because most full-thickness pressure ulcers do not usually close completely within 12 weeks [21], evaluating time to 100% closure is not always practical. Therefore, the primary outcome measures were prospectively defined as the incidence of 90% and 100% wound healing by 12 weeks, with 100% healing defined as complete epithelization of the wound. The time to healing was computed as the treatment period day during the weekly visit at which the surface area of the wound was noted as zero and completely healed. Average surface area reduction over time was calculated for each group. Adverse events were noted on the case report forms and were recorded at each visit.

2.6. Statistical analysis

Sample size was calculated using estimated healing rates of 27% for the standard of care arm and 47% for the SIS treatment group. Two groups of 69 patients each were required to demonstrate a 20% difference between the interventions, with $\alpha = 0.05$, power = 0.80. The total enrollment target was 140 patients (70 per group), of which 130 patients were eventually enrolled. Actual study power was therefore 0.78.

Study data were collected and entered into a study database by a Contract Research Organization (MED Institute, West Lafayette, IN) using quality control procedures. A quality assurance check of the database datasets versus the case report forms was performed. The database was transferred to a statistical services company (StatKing Consulting, Fairfield, OH) for independent analysis. All statistical analyses were performed using SAS software (version 8.2 for Windows, SAS Inc., Cary, NC) on the intent to treat population.

Frequency of 90% and 100% wound healing at 12 weeks in the SIS wound matrix and standard care treatment groups was analyzed using Fisher's Exact Test at the one-sided $\alpha = 0.05$ level of significance. Healing data were re-examined using baseline demographics and wound characteristics as covariates. These tests were conducted at the two-sided $\alpha = 0.05$ level of significance.

The difference in healing proportions, adjusting for each of the potential covariates, was tested using the Cochran-Mantel-Haenzel (CMH) Test and the Breslow-Day test of the homogeneity of odds ratios across strata. Time to healing was examined using a Cox proportional hazards regression model.

Continuous demographic and baseline variables were compared using ANOVA. A chi-square test was used to compare categorical demographic and baseline variable response profiles. Fisher's Exact Test was used to compare the proportion of patients in each treatment group experiencing adverse events.

3. Results

3.1. Patients

Although the nature of the treatment precluded blinding of the clinical staff, blind, prospective, randomization of study participants was used to eliminate bias in the assignment of treatment groups. There were no differences between the standard care and SIS wound matrix groups with respect to patient demographics and baseline ulcer size, stage, and duration (Table 2). Groups were also balanced in regard to additional patient health variables including: Type I diabetes (p = 0.62), Type II diabetes (p = 0.07), connective tissue disease (p = 0.96), immunosuppression (p = 1.0), peripheral vascular disease (p = 0.31), and dementia (p = 0.19). Overall, 15% (n = 19) of patients treated were home care, 27% (n = 35) were treated on an outpatient basis, and 58% (n = 75) were in long-term care.

Thirty-six (36) patients of the 130 (28%), 16 in the SIS wound matrix arm and 20 in the standard of care arm, did not complete the planned 12-week follow-up for reasons other than ulcer healing. These patients, however, were still included in the data analysis within their assigned group. The reasons for study non-completion are listed in Table 3.

Table 2
Baseline patient demographics.

	SIS (n = 67)	Control (n = 63)
Age, years, mean ± SEM (p = 0.11)	76 ± 2 Range: 24-97	78 ± 2 Range: 21-102
Gender (p = 0.99)		
Male (%)	35 (52%)	33 (52%)
Female (%)	32 (48%)	30 (48%)
Race (p = 0.71)		
Caucasian	55 (82%)	54 (86%)
Black	10 (15%)	7 (11%)
Other	2 (3%)	2 (3%)
BMI, mean ± SEM, (p = 0.71)	25.7 ± 0.8	25.2 ± 1.1
Range:	13.3–52.1	11.6–68.7
Ulcer Duration (p = 0.71)		
0–3 months	25 (37%)	28 (44%)
4–6 months	13 (19%)	13 (21%)
7–12 months	13 (19%)	10 (16%)
> 1 year	15 (22%)	10 (16%)
Unknown	1 (1%)	2 (3%)
Ulcer Area (cm^2), mean ± SEM, (p = 0.08)	6.8 ± 1.2	10 ± 1.6
Range:	1–63	1–60
Ulcer Stage (p = 0.64)		
Stage III	39 (58%)	33 (52%)
Stage IV	28 (42%)	28 (44%)
Unknown	0 (0%)	2 (3%)

3.2. Healing at 12 weeks

Complete healing at 12 weeks was measured as one of the primary study endpoints. Complete healing occurred in 40% (27/67) of patients receiving SIS wound matrix versus 29% (18/63) of patients receiving standard of care alone (Table 4). These results are not statistically significant (p = 0.111) using Fisher's Exact Test but show that the incidence of healing in the group treated with SIS wound matrix trends toward improvement as compared to standard of care alone.

Incidence of 90% wound reduction was also measured as a primary endpoint. Closure of 90% of the ulcer dimension occurred in 55% (37/67) of patients receiving SIS wound matrix versus 38% (24/63) of patients receiving standard of care alone (Table 5). These results are statistically significant (p = 0.037) using Fisher's Exact Test and show that when SIS is used in addition to standard of care, SIS leads to more complete wound closure than standard of care alone within 12 weeks.

Average wound surface area reduction was calculated for each group. While the rate of healing and average percent size reduction was not statistically different between groups, both groups achieved 35–40% surface area reduction within the first 3 weeks of treatment, but only the SIS wound matrix group progressed further to achieve an average of 65% surface area reduction over the 12-week treatment period (Fig. 1). These data indicate that the SIS wound matrix may foster a wound healing environment that allows even more refractive ulcers a greater chance of achieving complete closure than standard of care alone.

Assessment of wound healing after adjusting for potential covariates was performed as described but failed to generate any significant changes in the healing proportions of either group. Of particular interest, ulcer stage (p = 0.229), duration (p = 0.147) and initial ulcer size (p = 0.493) were not considered factors in the extent of healing observed. However, within 12 weeks, 49% of Stage III ulcers treated with SIS healed, while 29% of Stage IV ulcers treated with SIS healed; of the wounds with a surface area greater than 6 cm^2, 29% treated with SIS healed, but only 10% treated with standard of care healed (p = 0.124) (Table 6).

Table 3
Causes for patients not completing 12 week follow-up.

Reason	SIS Wound Matrix (n = 16)	Standard Care (n = 20)
Protocol non-compliance	2	1
Wound worsening and/or desired change in treatment	7	7
Lost to follow-up	2	8
Hospitalization and/or deteriorating patient health	4	1
Death	1	3

Table 4
Incidence of 100% healing at 12 weeks.

	Healed (%)[a]	Not Healed (%)
SIS	27 (40%)	40 (60%)
Standard Care	18 (29%)	45 (71%)

[a] p = 0.111 between treatment groups.

Table 5
Incidence of 90% healing at 12 weeks.

	Healed (%)[a]	Not Healed (%)
SIS	37 (55%)	30 (45%)
Standard Care	24 (38%)	39 (62%)

[a] p = 0.037 between treatment groups.

3.3. Six month follow-up

A total of 35 patients (29%) were seen at a 6-month follow-up visit, 21 in the SIS Wound Matrix group and 14 in the standard care group. Of these 35 patients, 17 had healed ulcers within the 12-week study period of treatment, and 15 of the 17 study ulcers remained healed at the 6-month follow-up visit: 8 of 10 (80%) in the SIS Wound Matrix group, and 7 of 7 (100%) in the standard care group. Of the other 18 patients with ulcers that did not heal within the 12-week study period, 2 patients were healed at the 6-month follow-up visit (2 of 11 patients in the SIS Wound Matrix group, 0 of 7 patients in the standard care group). Due to the small number of patients seen at the follow-up visit, no statistical analysis was performed.

Table 6
Healing at 12 weeks for different wound characteristics.

Ulcer Characteristic	% Healed		p-value
	SIS Wound Matrix	Standard Care	
Stage III	49%	36%	0.34
Stage IV	29%	21%	0.76
Size $< 6\,cm^2$	44%	45%	1.00
Size $\geq 6\,cm^2$	29%	10%	0.12
Duration < 6 mo	50%	37%	0.26
Duration ≥ 6 mo	25%	15%	0.49

Table 7
Postoperative complications[a].

Complication	SIS Wound Matrix (n = 11)	Standard Care (n = 12)
Skin injury/fissure	2	1
Hypoglycemia	1	–
GI Disorder	1	–
Urinary Tract Infection	–	1
Dermatitis	1	1
Osteomyelitis	1	–
Non-target wound infection	1	1
Wound Infection	3	5
Death	1	3

[a] p = 0.477 between treatment groups.

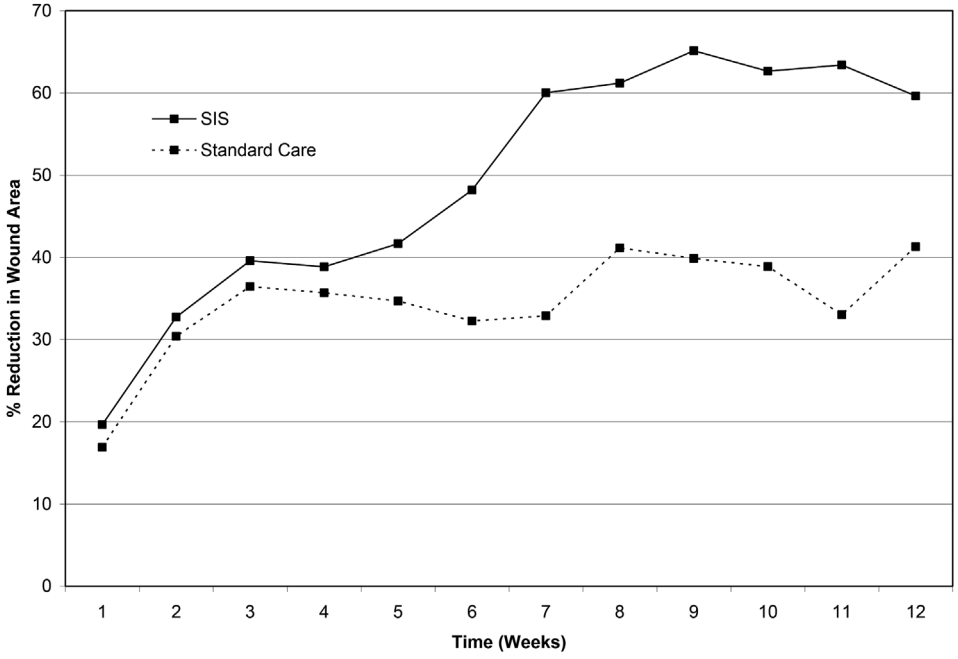

Fig. 1. Average Percent Reduction in surface Area Over Time.

3.4. Adverse events

The adverse events reported in this trial were typical for the patient population having hard-to-heal pressure ulcers. A total of 23 adverse events were observed (Table 7). There was no significant difference between the proportions of patients experiencing at least one adverse event during the study in the two treatment groups ($p = 0.477$). There was no significant difference between the proportions of patients experiencing any infection-related adverse event in the two treatment groups ($p = 0.483$).

4. Discussion

This multicenter, prospective, randomized clinical trial showed that although SIS wound matrix did not lead to significantly improved complete wound healing within 12 weeks versus standard of care, 40% of chronic wounds healed following treatment with SIS. Importantly, 12 week healing rates of 49% for Stage III pressure ulcers and 29% of Stage IV ulcers following SIS treatment is a significant improvement over historical standard of care success measures; only 40–45% healing for Stage III ulcers and 31–34% for Stage IV ulcers after 6 months has been reported in the literature [10,11], and suggests that significant reductions in patient morbidity and treatment costs, due to the rapid healing response observed, may be achieved when SIS is used in combination with standard of care treatment measures.

This study also demonstrated that treatment with SIS led to a greater overall reduction in ulcer surface area in 12 weeks than standard of care alone. Specifically, the data showed that SIS wound matrix led to a 90% ulcer area reduction in 55% of patients within 12 weeks, versus 38% of patients treated only with standard of care ($p = 0.037$). These results are important because decreased morbidity and substantial increases in the quality of life can be achieved with even modest reductions in pressure ulcer dimensions, even in the absence of complete healing [22,23].

Over time, literature has shown that patients can benefit considerably from achieving near-complete healing. Healing to 90% generally reflects granulation tissue formation and wound contraction and is a relatively rapid process that is followed by a slower, more sustained progression to complete epithelization [24,25]. In this trial, average reduction in ulcer size by 60% of baseline was achieved in the SIS wound matrix group by 7 weeks and progressed to 65% by 9 weeks, while average reduction of ulcer dimensions in the standard of care group never exceeded approximately 40%, even after 12 weeks. These results, although not statistically different, indicate that SIS wound matrix may foster a wound healing environment that leads to more complete closure by stimulating wound contraction and granulation tissue deposition, even in those wounds which may never achieve complete healing.

Treatment success often depends on pressure ulcer stage, baseline dimensions, and ulcer chronicity [2,11]. While the sample size available in this study was too small to support the historical data on a statistical basis, trends seen in this study agree with the historical data that smaller, less severe, and more acute wounds are more likely to heal, regardless of treatment protocol. One emerging trend, however, indicated that 29% of wounds greater than 6-cm [2] in baseline dimensions healed if they were treated with SIS wound matrix, but only 10% of these wounds healed with standard of care alone. These data suggest that the SIS wound matrix may hold a distinct advantage over standard of care treatments in healing pressure ulcers of larger dimensions.

A clear limitation of this study is that post-treatment follow-up was limited to 12 weeks, and an even-smaller number of patients were seen at a 6-month follow-up, which may be not be sufficiently long enough to allow for complete wound healing. Clearly, the limited number of wounds examined at the 6-month follow-up suggests that additional studies may be warranted to determine wound recurrence after treatment with SIS.

5. Conclusion

In conclusion, the results of this study suggest that within the setting of a comprehensive wound care program, weekly treatment of chronic pressure ulcers with SIS wound matrix increases the incidence of 90% healing versus standard of care alone and may be particularly advantageous in treating those ulcers of greater wound size that are less likely to heal with standard of care treatment measures. SIS wound matrix has an excellent safety profile and leads to healing of 40% of pressure ulcers in 12 weeks. Because standard of care has historically only achieved healing rates of 31–45% after 6 months, the addition of SIS wound matrix to a treatment program may speed healing, potentially reduce the costs associated with pressure ulcer treatment, and as a result, improve the quality of life of afflicted patients.

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Declarations of interest

Jason P. Hodde is an employee of Cook Biotech Incorporated.

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